Attorney Docket No.: 093580.010100

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: NORTON

SERIAL NO.: 10/735,180 **Group Art Unit:** 1623

FILED: December 12, 2003 **Examiner:** Olson, Eric

FOR: **DOSE-DENSITY AND SEQUENTIAL ADJUVANT CANCER CHEMOTHERAPY**

Commissioner for Patents
P.O. Box 1450
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Declaration of Larry Norton, M.D. Under 37 C.F.R. §1.132

I, Larry Norton, M.D., declare as follows:

1. I am the of the inventor of the invention disclosed in the present application.

2. I received my undergraduate degree from the University of Rochester in 1968 and my M.D. from Columbia University in 1972. I completed my residency in medical oncology in 1974 at Albert Einstein College of Medicine and a fellowship in medical oncology at the National Cancer Institute in 1976. I have been employed as a clinician and researcher by Memorial Sloan-Kettering Cancer Center since 1988 in the field of medical oncology.

3. I am a co-author of the article entitled "Sequential Adjuvant Therapy with Doxorubicin/Paclitaxel/Cyclophosphamide for Resectable Cancer Involving Four or More Axillary Nodes" published in *Seminars in Oncology* 22: 18-23 (1995) ("Hudis *et al.*").

4. I am co-author of the abstract for CALBG 9344 entitled "Improved disease-free survival from the addition of sequential paclitaxel (T) but not from the escalation of

doxorubicin (A) dose level in the adjuvant chemotherapy of patients with node-positive primary breast cancer" presented at the American Society of Clinical Oncology on May 18, 1998 (Proc *ASCO* 17:390a, 1998) ("Henderson *et al.*").

5. Unlike the current invention, Hudis *et al.* discloses a dose-intense treatment regimen with escalated doses, which resulted in both hematologic and non-hematologic toxicity.

6. Unlike the current invention, Henderson *et al.* discloses a conventional (i.e., non-dose-dense) therapy in which cyclophosphamide and doxorubicin were administered concurrently, followed by treatment with paclitaxel.

7. As noted in the specification, the invention is based on the findings of the INT C9741 cancer chemotherapy study.

8. As disclosed in Hudis et. al., before INT C9741, the expectation was that dose escalation of adjuvant therapy agents represented the likeliest route to improved survival from resected breast cancer and that dose reductions would compromise the effectiveness of the treatment.

9. The results of INT C9741 were, thus, remarkable and unexpected in that reduced doses of adjuvant therapy agents, given sequentially and in a dose-dense regimen, resulted in efficacious treatment.

10. Although the reduced doses disclosed in Henderson *et al.* were efficacious, there was no expectation, reasonable or otherwise, that those reduced doses, used in a sequential and does-dense regimen, would be efficacious. Under the medical ethics principle of equipoise, if the doses disclosed in Henderson *et al.* were more likely than not to be efficacious in a sequential and dose-dense regimen, proceeding with INT C9741 would have been unethical. The principle of equipoise stands for the proposition that a

subject should only be submitted to a randomized, controlled experiment if there is substantial uncertainty about whether a treatment would benefit the subject. In mathematical terms, equipoise requires that, prior to a study, the probability for either treatment A or treatment B being superior to the other is 50%.

11. Indeed, if the doses disclosed in Henderson *et al.* were more likely than not to be efficacious in a sequential and dose-dense regimen, the National Cancer Institute would never have allowed the INT C9741 study to go forward.

12. The use of an optimal amount of a chemotherapeutic agent in a sequential and/or dose dense regimen with other agents may not necessarily result in a successful clinical result due to factors such as unexpected toxicities, unexpected interactions of the agents and feasibility in terms of detrimental impact on the quality of life (e.g., loss of libido and loss of muscle mass).

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity or enforceability of the present application or any patent issued thereon.

Larry Norton, M.D.

4/16/07
Date